USE OF ASPIRIN VERSUS ANTICOAGULANTS IN THE TREATMENT OF PATIENTS WITH MYOCARDIAL INFARCTION AFTER STREPTOKINASE THERAPY

THESIS

SUBMITTED FOR PARTIAL FULFILMENT OF MASTER DEGREE IN CARDIOLOGY

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1991

ACKNOWLEDGEMENT

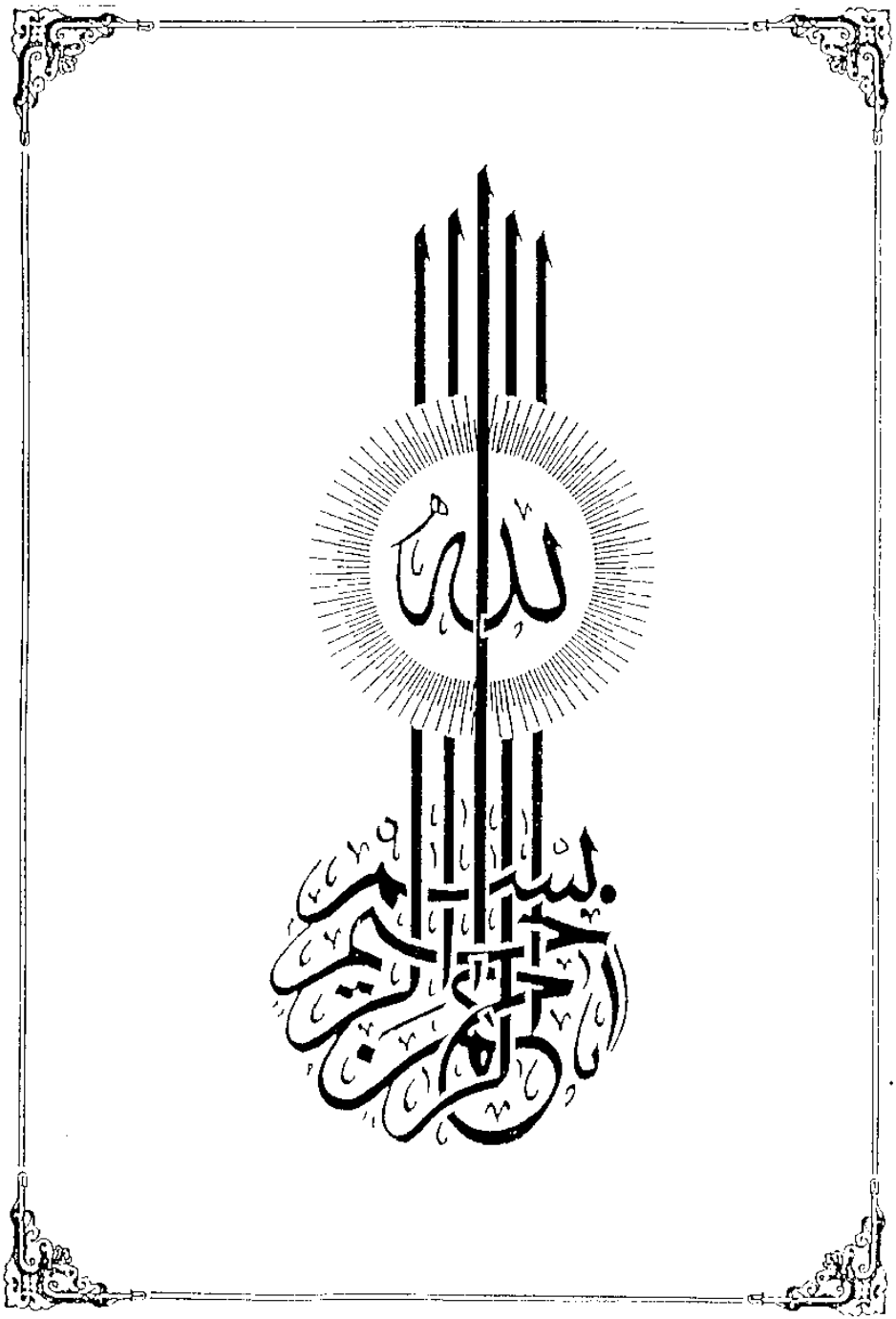
It is a great honour to me to express my deep gratitude to :

* Professor Doctor / RAMEZ RAOUF GUINDY

* Doctor / EGLAL ABDEL AZIZ EL GHOBASHI

For their teaching , valuable advice, wise guidance, kind supervision and continuous encouragement throughout this work .

MOUSHIR M.FADL



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INTRODUCTION

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Myocardial infarction can occur in patients with long standing angina pectoris, or conversely, be a sudden event in patients who are either asymptomatic or with recent onset angina.

The major determinant of the outcome following myocardial infarction is the extent of myocardial damage. Myocardial infarction is a dynamic process evolving over several hours. During these hours, early interventions may reduce the extent of myocardial necrosis, if they can alter the continuing imbalance between myocardial oxygen supply and metabolic demand caused by the acute interruption of coronary blood flow.

Most attempts to limit infarct size have attempted to do so by reduction of oxygen demand with acute interventions such as beta blockers, nitroglycerin, calcium channel blockers and intra-aortic balloon conterpulsations. Attempts to improve oxygen supply acutely, such as emergency peri-infarction coronary bypass surgery, have been shown to be technically feasible and effective for preserving myocardial function on a long term basis. However, the personnel and financial resources necessary to perform emergency coronary bypass within the first few hours of myocardial infarction limit this form of therapy.

Time is a crucial element in any attempt to salvage the myocardium, and it would be difficult to provide prompt emergency surgery for large numbers of critically ill patients. Alternative means to revascularise the myocardium are desirable.

Another direct approach to improvement of coronary blood flow in acute myocardial infarction is lysis of the acute intracoronary thrombus. Thrombolytic therapy is gaining acceptance as a method of reducing mortality in acute myocardial infarction. In patients with evolving acute myocardial infarction, administration of streptokinase by the intracoronary, and more recently, the intravenous route, has been shown to be an effective means of reopening the acutely occluded coronary artery and restoring antegrade blood flow.

The earlier the treatment is instituted, the larger the benefit in terms of survival and left ventricular function.

In the majority of patients successfully treated with streptokinase, a significant stenosis remains at the site of previous thrombolysed occlusion, as platelet activity is known to be increased in acute myocardial infarction, and is increased still further by fibrinolytic therapy.

Reocclusion and reinfarction have been reported to occur in 7% to 29% of patients after treatment with intravenous streptokinase *[George A., 1988]*

Antiplatelets, as well as anticoagulants, play an important role in providing protection against reocclusion after treatment with streptokinase:-

* Aspirin is the most convenient and widely tested antiplatelet, it irreversibly inhibits cyclo-oxygenase dependant platelet aggregation, thereby inhibiting thromboxane A_2 synthesis.
* Full dose anticoagulation with heparin or oral anticoagulants may provide protection against reocclusion by allowing time for potential collaterals to form.

So, in principle, any early benefits after streptokinase therapy might not persist, unless reocclusion can be avoided, perhaps by anticoagulants or antiplatelet agents.

Aim of work

The aim of this work is to evaluate the effect of aspirin, the most widely used antiplatelet, in comparison to that of anticoagulants in patients with myocardial infarction after successful treatment with streptokinase, regarding:-

* Clinical prognosis

* Recurrence of coronary occlusion and myocardial infarction.

THROMBOLYTIC THERAPY

THROMBOLYTIC THERAPY

* History

* Mode of action

* Patient selection

* Data of successful thrombolysis.

History of thrombolytic therapy:

Streptokinase is a purified exotoxin of group CB-hemolytic streptococci.Tillet and Garner first demonstrated the fibrinolytic activity of hemolytic streptococci in 1933. Tillet and Scherry first used streptokinase in humans to aid resolution of hemothorax and empyema. Subsequently, in 1959, Fletcher and colleagues applied intravenous streptokinase infusions to patients with myocardial infarction, pulmonary embolism and deep venous thrombosis.

In the case of myocardial infarction, 22 patients were treated within 16 hours of onset of pain. Their end point was change in kinetics of SGOT washout. They observed that the peak of SGOT rise occurred earlier than one would have expected and

later values were lower than one would have expected during a typical course of myocardial infarction. Obviously, these data are inconclusive but suggest that SGOT could have washed out of an area of myocardium that have undergone successful reperfusion.

Infusions of a fibrinolytic agent directly into the ascending aorta during acute myocardial infarction followed in 1960 but did not employ coronary angiography to document abolition of thrombi *[Gold HK., 1983]*

Intravenous infusion of streptokinase was studied in many medical centers in Europe, different protocols being used throughout the 1960s and 1970s. The results of these studies are difficult to interpret because of varying criteria for patient selection , as well as the unkown extent of myocardial infarction and underlying coronary artery disease.

The European Cooperative study group for streptokinase treatment in acute myocardial infarction, which was conducted in 11 European centers, randomized patients to treatment within 24 hours of either intravenous streptokinase infusion or dextrose infusion (Control). The group treated with streptokinase had a significantly lower mortality both on immediate follow up and six months after treatment *[Thomas A., 1984]*

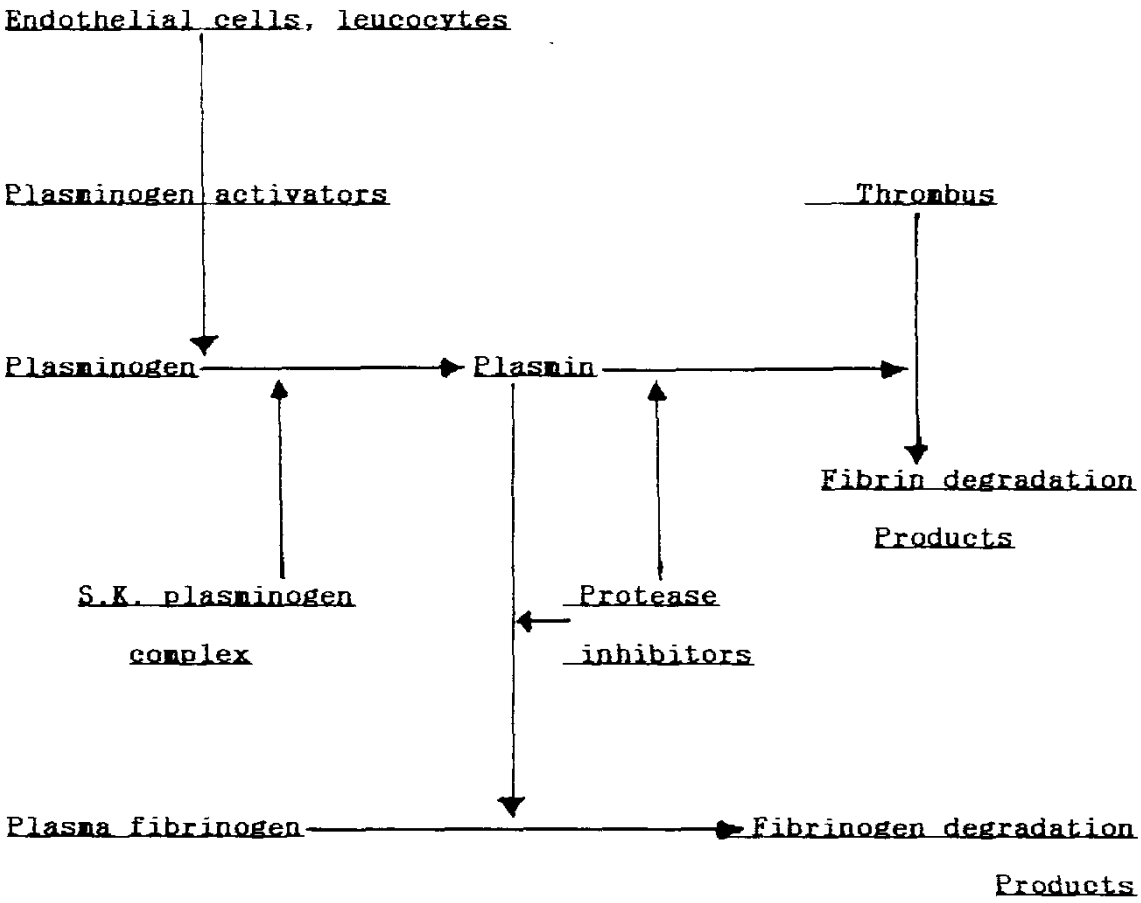
Several subsequent studies in Germany and the United states, using different protocols, achieved similar results. Later, other reports confirmed this early experience and demonstrated variable myocardial salvage assessed by different techniques. Early in 1982, the Food and Drug Administration approved streptokinase therapy for acute myocardial infarction.

Mode of action:

Streptokinase dissolves thrombi by activating plasminogen forming plasminogen activator complex, thereby generating plasmin, a plasma protein that lyses fibrin and degrades fibrinogen, prothrombin and activated factors V and VIII.

Streptokinase converts both circulating and fibrin bound plasminogen to plasmin, producing low levels of circulating fibrinogen and high titres of fibrinogen degradation products that have prolonged anticoagulant properties. Therefore a low fibrinogen level can be used as a clinical marker of a systemic lytic state. *[Carl W., 1989]*

The following figure shows the endogenous fibrinolytic system and site of action of streptokinase:-



(Bastway A., 1987)

The most commonly used clinical dose is: 1.5 million units over 30 - 60 minutes. This brief duration of infusion of streptokinase refers to its very short half life: 23 minutes .

Thus, since intracoronary thrombosis usually initiates myocardial infarction, thrombolysis restores infarct artery patency.

It was found that arterial patency preserves left ventricular function, which is a determinant factor in survival and quality of life. *[Topol EF., 1987]*

Patient Selection :

Many factors must be considered in patient selection for thrombolytic therapy in acute myocardial infarction.

First of all, since the goal of thrombolytic therapy is not only to re-establish blood flow through the occluded coronary artery, but also to salvage significant amounts of myocardium destined to undergo necrosis, the early institution of therapy is of the utmost importance. The extent of myocardial necrosis depends on several factors:

1- The degree of occlusion
2- The presence and extent of functioning collateral circulation
3- Factors affecting myocardial metabolism.
4- The time interval from occlusion to restoration of coronary blood flow.